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(71) Applicant *(for all designated States except US)*: **ISTITUTO SUPERIORE DI SANITA'** [IT/IT]; Viale Regina Elena, 299, I-00161 Roma (IT).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **ENSOLI, Barbara** [IT/IT]; Via Monte Pollino, 2, I-00141 Rome (IT).

(74) Agent: **GERVASI, Gemma**; Notarbartolo & Gervasi, Corso di Porta Vittoria, 9, I-20122 Milan (IT).

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— *of inventorship (Rule 4.17(iv)) for US only*

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— *with amended claims*

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

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(54) Title: USE OF HIV-PROTEASE INHIBITORS TO BLOCK CELL MIGRATION AND/OR INVASION, TISSUE INFILTRATION AND OEDEMA FORMATION

(57) Abstract: The present invention relates to a method to block the invasion of normal, neoplastic inflammatory or immune cells, tissue infiltration, and/or oedema formation through inhibition or modulation of molecules and proteolytic enzymes such as -but not exclusively- MMPs, for the therapy of all diseases whose pathogenesis is related to the above processes, including tumours, non-neoplastic angioproliferative diseases, inflammatory diseases, or autoimmune diseases, the method being based on the use of inhibitors of the protease of the HIV virus (HIV-PI).

AMENDED CLAIMS

[received by the International Bureau on 19 December 2002 (19.12.02)
Claims 1-27 replaced by new claims 1-26]

CLAIMS - Art. 19PCT

1. Use of at least one compound selected in the group of the inhibitors of the protease of the HIV virus, HIV-PI, for the preparation of a medicament for treating a subject suffering from or susceptible to a condition which can be treated or prevented by blocking the migration/invasion of cells selected in the group of: endothelial, neoplastic, inflammatory or immune cells.
2. Use according to claim 1 wherein cell migration/invasion results in tissue infiltration and/or oedema formation.
3. Use according to claims 1-2 wherein the block is obtained through inhibition or modulation of molecules and proteolytic enzymes selected in the group of: MMPs including MMP-2, stromelysins and matrilysin; enzymes activating MMPs; thrombospondin; bFGF and VEGF alone or associated between them, Tat alone or in the presence of bFGF.
4. Use according to claim 3 in which the proteolytic enzymes are MMPs.
5. Use according to claims 1-4 wherein the condition to be treated or prevented is at least one of the following pathologies: inflammatory, autoimmune, neoplastic, non-neoplastic angioproliferative diseases.
6. Use according to claims 1-6 wherein the HIV-PI has an anti-angiogenic, anti-tumour, anti-oedemigenic and/or anti-inflammatory activity for the treatment of KS, tumours and non-neoplastic angioproliferative, inflammatory and autoimmune diseases.
7. Use according to claims 1-6 wherein the HIV-PI is selected among the following compounds: indinavir, saquinavir, ritonavir, nelfinavir, amprenavir, lopinavir and ritonavir, corresponding pharmaceutically acceptable derivatives and chemical analogues, and mixtures thereof.
8. Use according to claim 7 wherein the compounds are administered at the following doses: indinavir: 600 mg/day, 1200 mg/day, 2400 mg/day and 4800 mg/day; saquinavir: 900 mg/day; 1800 mg/day, 3600 mg/day, 7200 mg/day
9. Use according to claims 1-8 wherein the pathological condition is selected in the group of: Kaposi's sarcoma, angiogenesis; non-neoplastic angioproliferative diseases of eye, kidney, vascular system, skin, such as, for example, diabetic retinopathy, retrolental fibroplasia, trachoma, vascular

glaucoma, psoriasis, immune and non-immune inflammation, atherosclerosis, keloids; benign and malignant tumours of the soft tissues, the cartilages, the bones and the blood; autoimmune diseases in general, in particular systemic lupus erythematosus, scleroderma, rheumatoid arthritis, psoriasis, thyroiditis, ulcerous rectocolitis and Crohn's disease, Goodpasture's syndrome, systemic vasculitis, Sjögren's syndrome, primitive billary cirrhosis; inflammatory diseases, in particular chronic inflammation associated with allergies and with viral infective, bacterial or parasitic agents, including the Castleman's multicentric disease.

10. Use according to claim 9 wherein the HIV-PI is in association with anti-inflammatory, anti-angiogenic or anti-tumour drugs.

11. Use according to claims 1-10 in subjects infected or not infected by HIV.

12. Use according to claims 1-11 wherein the drug is administered according to a procedure selected among; oral, intravenous, intramuscular, subcutaneous, intradermal, intraperitoneal, intrathecal, intrapleural, intrauterine, transmucosal, rectal, vaginal, intralesional or percutaneous administration.

13. Method for modulating biological processes involving cell migration and invasion, tissue infiltration and activity of molecules involved in these cell pathways, including MMPs and thrombospondin, said method comprising the administration of an effective amount of at least one compound selected in the group of the inhibitors of the protease of the HIV virus, HIV-PI.

14. Method for treating pathological conditions involving cell migration and invasion, tissue infiltration and activity of molecules involved in these cell pathways, including MMPs and thrombospondin, said method comprising the administration of a therapeutically effective amount of at least one compound selected in the group of the inhibitors of the protease of the HIV virus, HIV-PI.

15. Method for treating a subject suffering from or susceptible to a condition which can be treated or prevented by blocking the migration/invasion of cells selected in the group of: endothelial, neoplastic, inflammatory or immune cells, said method comprising the administration of a therapeutically effective amount of at least one compound selected in the group of the inhibitors of the protease of the HIV virus, HIV-PI.

16. Method according to claim 15 wherein cell migration/invasion results in tissue infiltration and/or oedema formation.

17. Method according to claim 15 wherein the block is obtained through inhibition or modulation of molecules and proteolytic enzymes selected in the group of: MMPs including MMP-2, stromelysins and matrilysin; enzymes activating MMPs; thrombospondin; bFGF and VEGF alone or associated between them, Tat alone or in the presence of bFGF.

18. Method according to claim 17 wherein the proteolytic enzymes are MMPs.

19. Method according to claim 15 wherein the condition to be treated or prevented is at least one of the following pathologies: inflammatory, autoimmune, neoplastic, non-neoplastic angioproliferative diseases.

20. Method according to claim 15 wherein the HIV-PI has an anti-angiogenic, anti-tumour, anti-oedemigenic and/or anti-inflammatory activity for the treatment of KS, tumours and non-neoplastic angioproliferative, inflammatory and autoimmune diseases.

21. Method according to claim 15 wherein the HIV-PI is selected among the following compounds: indinavir, saquinavir, ritonavir, nelfinavir, amprenavir, lopinavir and ritonavir, corresponding pharmaceutically acceptable derivatives and chemical analogues, and mixtures thereof.

22. Method according to claim 21 wherein the compounds are administered at the following doses: indinavir: 600 mg/day, 1200 mg/day, 2400 mg/day and 4800 mg/day; saquinavir: 900 mg/day; 1800 mg/day, 3600 mg/day, 7200 mg/day

23. Method according to claim 15 wherein the pathological condition is selected in the group of: Kaposi's sarcoma, angiogenesis; non-neoplastic angioproliferative diseases of eye, kidney, vascular system, skin, such as, for example, diabetic retinopathy, retrolental fibroplasia, trachoma, vascular glaucoma, psoriasis, immune and non-immune inflammation, atherosclerosis, keloids; benign and malignant tumours of the soft tissues, the cartilages, the bones and the blood; autoimmune diseases in general, in particular systemic lupus erythematosus, scleroderma, rheumatoid arthritis, psoriasis, thyroiditis, ulcerous rectocolitis and Crohn's disease, Goodpasture's syndrome, systemic vasculitis, Sjögren's syndrome, primitive billary cirrhosis; inflammatory

diseases, in particular chronic inflammation associated with allergies and with viral infective, bacterial or parasitic agents, including the Castleman's multicentric disease.

24. Method according to claim 15 wherein the HIV-PI is in association with anti-inflammatory, anti-angiogenic or anti-tumour drugs.

25. Method according to claim 15 wherein the subjects are subjects infected or not infected by HIV.

26. Method according to claim 15 wherein the drug is administered according to a procedure selected among: oral, intravenous, intramuscular, subcutaneous, intradermal, intraperitoneal, intrathecal, intrapleural, intrauterine, transmucosal, rectal, vaginal, intralesional or percutaneous administration.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/04303

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/4725 A61K31/496 A61P35/00 A61P17/06 A61P9/10
A61P37/06 A61P1/00 A61P37/08 A61K38/55 A61K31/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 33654 A (UNIV MARYLAND BIOTECH INST) 15 June 2000 (2000-06-15) cited in the application page 1, line 12-17; claims 7,9 page 10, line 8-25 page 11, line 17-21 page 19, line 2-4 page 29, line 12-19 page 34, line 25-28 page 37, line 20-23 -/-	1-27

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 October 2002	22/10/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Allnutt, S

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CONANT M A: "REDUCTION OF KAPOSI'S SACROMA LESIONS FOLLOWING TREATMENT OF AIDS WITH RITONOVIR" AIDS, LONDON, GB, vol. 11, no. 10, August 1997 (1997-08), pages 1300-1301, XP000983605 ISSN: 0269-9370 see whole document	1-27
X	WO 99 63998 A (GROETTRUP MARCUS ;ZINKERNAGEL ROLF (CH); INST NAT SANTE RECH MED () 16 December 1999 (1999-12-16) page 1, line 24-34; example 3 claims 1-5,8-10 page 3, line 11-23	1-27
X	BERTHELOT P ET AL: "Dramatic cutaneous psoriasis improvement in a patient with the human immunodeficiency virus treated with 2',3'-dideoxy,3'-thyacytidine 'correction of 2',3'-dideoxycytidine! and ritonavir 'letter! 'published erratum appears in Arch Dermatol 1998 Apr;134(4):452!" ARCHIVES OF DERMATOLOGY, XX, XX, vol. 133, no. 4, 1 April 1997 (1997-04-01), page 531,452 XP002095182 ISSN: 0003-987X see whole document	1-27
X	ANDRE ET AL: "An inhibitor of HIV-1 protease modulates proteasome activity, antigen presentation, and T cell responses" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, NATIONAL ACADEMY OF SCIENCE. WASHINGTON, US, vol. 95, no. 22, 1 October 1998 (1998-10-01), pages 13120-13124, XP002095181 ISSN: 0027-8424 See abstract	1-27
P,X	SGADARI C; BARILLARI G; TOSCHI E; ET AL: "HIV protease inhibitors are potent anti-angiogenic molecules and promote regression of Kaposi sarcoma" NATURE MEDICINE, vol. 8, no. 3, March 2002 (2002-03), pages 225-232, XP002214286 see whole document	1-27

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 02/04303

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 16-27 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 1-10,16-26
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [X] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-27 (all in part)

   The treatment of neoplastic diseases

2. Claims: 1-27 (all in part)

   The treatment of inflammatory diseases

3. Claims: 1-27 (all in part)

   The treatment of immune diseases

4. Claims: 1-27 (all in part)

   The treatment of non-neoplastic diseases excluding those in subjects 1-3.
   i.e. non-neoplastic angioproliferative diseases

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-10,16-26

1. In claim 1, the expression "for blocking the migration/invasion of cells" is defined by reference to a desirable characteristic or property. In addition, it is considered unclear as it does not provide an indication for a pathological disorder nor define a disease state. Such is not a method of therapy according to R.67.1(iv) PCT as the intended disease(s), disorder(s) or dysfunction(s) to be treated are not defined. Accordingly, since a meaningful search over the whole of the claimed scope is impossible, the search has thus been restricted to the specific diseases defined in claim 27.
The same reasoning applies to claim 2.

2. If a therapeutic use is intended within the meaning of claim 1, the inclusion of "normal cells" leads to a lack of clarity within the meaning of Art 6 PCT. Methods of treatment must have a therapeutic use. Infact migration/invasion of normal cells can occur in the absence of a disorder e.g. blood cells.

3. In claims 3-5, the expressions "blocking the migration of endothelial cells with a therapeutic anti-angiogenic, anti-KS and anti-tumor effect.....blocking the production of cytokines with a therapeutic anti-tumor effect; inhibition or modulation of molecules and proteolytic enzymes" are defined by reference to a desirable characteristic or property. They do not relate to diseases, disorders or dysfunctions but rather mechanisms involved in an extremely large number of possible diseases. In fact, these claims are defined in such a way that a lack of clarity and/or conciseness within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search over the whole of the claimed scope impossible.
Although the diseases are further defined in claims 6-8 and 10, they are still none the less considered to encompass too large a number of possible diseases.
Consequently, the search has been carried out for those parts of the claims which do appear to be clear and/or concise, namely for the treatment of the diseases mentioned in claim 27.

4. The expression "HIV-protease inhibitors" is defined by reference to a desirable characteristic or property. This leads to a lack of clarity (Article 6 PCT) and is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently a search has been carried out for those clear, suported and concise claims i.e. the compounds defined in claim 11.
In addition, this term encompasses a very large number of possible compounds which may have this characteristic and a complete search is therefore not possible. The applicants attentions is drawn to the fact that some compounds may be already known to treat the diseases/disorders claimed by the applicant but are as yet not identified as HIV-Protease inhibitors.
In claim 9, the expression "has an anti-oedemigenic activity" is defined by reference to a desirable characteristic or property. This leads to a

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

lack of clarity (Article 6 PCT) and is such as to render a meaningful search over the whole of the claimed scope impossible.

5. The expressions "anti-inflammatory, anti-angiogenic or anti-tumour drugs" encompass a very large number of possible compounds which may have these characteristics and a complete search is therefore not possible. These terms do not appear to be clear or supported, therefore a complete search was unable to be carried out.

6. Present claims 16-18 are directed to a method of treatment, as they encompass the administration of active agents to patients. However, the intended purpose is defined by reference to a desirable characteristic or property, namely "for modulating/blocking.....". Such is not a method of therapy according to R.67.1(iv) PCT as the intended disease(s), disorder(s) or dysfunction(s) to be treated is/are not defined.
Claims 16-26 cover all methods having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT only for a limited number of such methods.
Accordingly, since a meaningful search over the whole of the claimed scope is impossible, the search has thus been restricted to those diseases that are clearly defined.
Although the diseases are further defined in claims 22, 24 and 26 they are still none the less considered to encompass too large a number of possible diseases. Consequently, the search has been carried out for those parts of the claims which do appear to be clear and/or concise, namely for the use of at least one HIV-protease inhibitor (see item 4) for treatment of the diseases mentioned in claim 27.

ACCORDINGLY: WITH RESPECT TO POINTS 1-6, THE SEARCH HAS BEEN CARRIED OUT BASED ON THE USE OF COMPOUNDS DISCLOSED IN CLAIM 11, FOR THE TREATMENT OF DISEASES DISCLOSED IN CLAIM 27.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

national Application No
PCT/EP 02/04303

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0033654 A	15-06-2000	AU 1930900 A	26-06-2000
		WO 0033654 A1	15-06-2000
WO 9963998 A	16-12-1999	FR 2779653 A1	17-12-1999
		AU 4049399 A	30-12-1999
		EP 1083898 A1	21-03-2001
		WO 9963998 A1	16-12-1999
		JP 2002517441 T	18-06-2002